Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly

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Object. The results of surgical therapy for acromegaly were assessed using carefully conducted endocrinological testing in 115 patients who underwent transsphenoidal surgery from 1981 to 1995.

Methods. Ninety-nine of the 115 patients could be contacted for follow-up review; in 57 of the patients an endocrinological assessment was performed by the authors. Biochemical cure was strictly defined as a normalization of the insulin-like growth factor (IGF)-I level (obtained in 100 patients) and/or a basal or glucose-suppressed growth hormone (GH) level of 2 ng/ml or less. The mean length of follow up from transsphenoidal surgery to laboratory testing was 5.4 years with a maximum of 15.7 years. After transsphenoidal surgery alone, 61% of the patients achieved a biochemical remission; the remission rate was 88% for patients with microadenomas and 53% for those with macroadenomas. Tumor size and preoperative GH level tended to correlate negatively with outcome of surgery. Early postoperative GH level tended to correlate with long-term outcome; in cases in which the early postoperative GH level was lower than 3 ng/ml, the chance of long-term remission was 89%. Thirty-two patients received postoperative radiotherapy: in 10 (31%) of these patients the disease is currently in remission after surgery and radiotherapy only and in three others the disease is in remission with the addition of medical therapy. The overall complication rate was 6.9% with no cerebrospinal fluid leaks, meningitis, permanent diabetes insipidus, or new hypopituitarism. The overall recurrence rate was low at 5.4%.

Conclusions. This series shows, based on IGF-I measurements and strict GH suppression criteria to define remission, that transsphenoidal surgery provides an excellent chance for long-term cure in patients with microadenomas. Surgery alone is successful in most patients with noninvasive macroadenomas; however, most patients with invasive macroadenomas will require adjunctive therapy. Recurrences are uncommon when biochemical remission is clearly documented postoperatively.

KEY WORDS • acromegaly • pituitary adenoma • transsphenoidal surgery • growth hormone • insulin-like growth factor–I

Acromegaly is a disorder characterized by excessive growth hormone (GH) secretion, which in almost all cases is caused by a GH-secreting pituitary adenoma. An excess of GH can lead to significant morbidity largely caused by the development of cardiovascular disease, musculoskeletal deformity, diabetes mellitus, and an increased incidence of malignancy. Transsphenoidal surgery for removal of the pituitary adenoma is the first form of therapy offered to most patients. Reports of most previous transsphenoidal surgical series have listed surgical cure rates between 60% and 70%, with surgical results being considerably better for microadenomas. Although in most series the cure rate has been examined based on postoperative GH levels lower than 5 ng/ml, strict criteria for biochemical cure in cases of acromegaly are now generally considered to be a glucose-suppressed GH of less than 2 ng/ml and a normalization of insulin-like growth factor (IGF)-I. In only a few large series has outcome been examined with a modern IGF-I assay. Therefore, we conducted a follow-up evaluation in a large cohort of patients who underwent transsphenoidal surgery for acromegaly performed by the senior author (K.D.P.) from 1981 to 1995 to determine endocrinological outcome based on IGF-I levels and/or glucose-suppressed GH levels after transsphenoidal surgery in this cohort of patients.

Clinical Material and Methods

Patient Population

From January 1981 to December 1995, 125 patients underwent transsphenoidal surgery for acromegaly. Acromegaly was defined preoperatively as a GH nadir greater than 2 ng/ml after oral glucose suppression testing and/or an elevated IGF-I level with the presence of a sellar mass on the imaging study. All patients had pathological confirmation of a GH-secreting pituitary tumor at surgery. There were 62 women and 63 men in the series with a mean age of 45 years (range 20–86 years). The patients’ mean preoperative GH level was 49 ng/ml with a range of 3.5 to 800 ng/ml. Prolactin levels were elevated to higher
than 20 ng/ml in 38 patients (range 26–3400 ng/ml). Eight patients received prior surgical therapy elsewhere; one of these had also received radiotherapy previously. Preoperatively 21% of the patients had received medical therapy prescribed by their physician; 11% had received octreotide and 10% received a dopamine agonist. Based on preoperative measurement of the morning cortisol level, thyroid functions, luteinizing hormone and follicle-stimulating hormone levels, testosterone level in men, and menstrual history in women, 36 (31%) of the patients had preoperative evidence of impaired anterior pituitary function: two had panhypopituitarism; 28 had hypogonadism only (secondary amenorrhea in women or low testosterone levels in men); five had hypothyroidism only; and one had isolated secondary adrenal insufficiency. Tumor size was determined from preoperative computerized tomography or magnetic resonance imaging. A microadenoma was defined as a tumor measuring 10 mm or less and a macroadenoma a tumor measuring more than 10 mm. There were 98 microadenomas and 27 microadenomas.

All patients underwent transphenoidal microsurgical adenomectomy via a transnasal approach. Gross-total removal was attempted at every procedure. The extent of tumor invasion and the extent of resection were ascertained by the surgeon. No patient underwent a hypophysectomy.

Thirty-two patients underwent postoperative radiotherapy: 28 had conventional fractionated radiotherapy; two had stereotactic radiosurgery; and one had proton-beam radiotherapy. Radiotherapy was administered for persistent biochemical evidence of acromegaly in all 32 patients and in all but two patients for clear residual pituitary or parasellar tumor.

Other than GH levels, postoperative pituitary function was assessed based on data obtained from the patients’ primary physician and a medication history obtained at the time of the follow-up assessment.

Study Design

The medical records of all patients were reviewed in detail and all clinical, laboratory, radiographic, pathological, and radiotherapeutic data were collected. All available follow-up laboratory data and history were also recorded from the medical records. Ten patients were excluded from the analysis of surgical outcome; eight of these patients had undergone prior surgery or radiotherapy elsewhere and two had no available postoperative GH levels.

Patients were contacted by letter and later by telephone and invited to come for one visit with us; the visit consisted of an interview, physical examination, and laboratory testing. Laboratory testing consisted of blood sampling at 9 a.m. for GH and IGF-I levels, after an overnight fast, and additional testing of GH levels at 60, 90, and 120 minutes after the patient drank 100 g of oral glucose. The glucose-suppressed GH value was considered to be the nadir level of GH measured at any time after administration of the oral glucose. A total of 57 patients came to us for the full evaluation.

For patients who were unable to come for a visit, the results of their most recent GH and IGF-I levels and their intervening history were obtained from their physician; these data were used in assessing disease status.

Results

Follow-Up Assessment

A current assessment of disease status (within the last year) was obtained in 99 patients. In 57 of these patients, laboratory testing, consisting of measurement of IGF-I and basal and glucose-suppressed GH levels, was completed. In 42 patients the results of recent blood testing for GH and IGF-I levels were obtained from their physician. Recent follow-up data were not available in 16 patients, and, in these patients, the results of their most recent IGF-I or GH tests were used to determine outcome after transphenoidal surgery. Four of these 16 patients died: two of complications related to acromegaly, one as a result of carcinoma, and one of an unrelated infection. The IGF-I levels were available in 100 patients and were used for data analysis. In the remaining 15 patients only basal and glu-
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TABLE 1
Current status of disease in 115 postoperative patients who underwent transsphenoidal surgery for acromegaly*

<table>
<thead>
<tr>
<th>Factor</th>
<th>All Tumors</th>
<th>Microadenomas</th>
<th>Macroadenomas</th>
<th>Noninvasive Macroadenomas</th>
<th>Invasive Macroadenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no. of patients</td>
<td>115</td>
<td>25</td>
<td>90</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>remission w/ surgery only</td>
<td>70 (61%)</td>
<td>22 (88%)</td>
<td>48 (53%)</td>
<td>38 (67%)</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>remission (all therapy)</td>
<td>82 (71%)</td>
<td>23 (92%)</td>
<td>59 (66%)</td>
<td>45 (79%)</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>received RT/remission w/ RT</td>
<td>32/11</td>
<td>1/1</td>
<td>31/10</td>
<td>11/7</td>
<td>16/4</td>
</tr>
<tr>
<td>currently receiving BC or octr/</td>
<td>15/4</td>
<td>1/1</td>
<td>14/3</td>
<td>6/2</td>
<td>8/1</td>
</tr>
<tr>
<td>remission w/ BC or octr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* BC = bromocriptine therapy; octr = octreotide; RT = postoperative radiotherapy.

cose-suppressed GH values were available and these were used in the data analysis. Seven of these patients had a glucose-suppressed GH level of 2 ng/ml or less and their disease was considered to be in remission; six had basal GH levels higher than 3.5 ng/ml (range 3.5–150 ng/ml) with residual tumor on magnetic resonance imaging and were considered to have active disease; and two patients (one with a macroadenoma and one with a microadenoma) had basal GH levels on two or more occasions that were lower than 1 ng/ml (range 0.5–0.7 ng/ml) with no visible residual tumor and their disease was considered to be in remission.

In the 57 patients in whom we measured concurrent IGF-I and glucose-suppressed GH values, the results were concordant in 50 patients. In five patients, the IGF-I levels were normal, but the glucose-suppressed GH levels measured with our RIA were between 2 and 3 ng/ml. These patients' disease was considered to be in remission. Conversely, in two patients the level of IGF-I was clearly elevated, but the level of GH fell to 2 ng/ml after glucose intake, and these two patients were considered to have active disease.

The average length of the follow-up period from transsphenoidal surgery to laboratory testing was 5.4 years with a range of 1 week to 15.7 years. The median follow-up period was 4.9 years. The follow-up period was at least 1 year in 102 patients, 3 years or longer in 73 patients, and 5 years or longer in 56 patients.

**Surgical Results**

The results of transsphenoidal surgery in the 115 patients from this series are reported in Table 1 and Fig. 1. Biochemical remission was achieved in 61% of all patients who underwent transsphenoidal surgery alone. Remission after surgery and adjunctive therapy was achieved in 71% of all patients. Of these 115 patients, 25 had microadenomas. The remission rate for surgery alone was 88% for cases of microadenomas. One patient with a microadenoma is also in remission after additional radiotherapy and concurrent medical therapy. Ninety patients had macroadenomas. The remission rate for macroadenomas treated by surgery alone was 53%. Sixty-six percent of the macroadenoma cases are currently in remission after the patients underwent surgery and adjuvant therapy. Patients with noninvasive macroadenomas had a substantially better outcome after transsphenoidal surgery than those with invasive macroadenomas (67% compared with 30%).

A second surgical procedure was performed in 12 patients. Ten underwent repeated transsphenoidal surgery for a recurrent tumor and in nine of the 10 the residual tumor was resected. In one case no tumor was found and was presumed to be located in the cavernous sinus. Two patients underwent a craniotomy for residual suprasellar tumor and symptoms of compression. Remission was achieved in four patients after the second surgical procedure, in two of these patients after the addition of radiotherapy.

Surgical complications included one case of transient postoperative syndrome of inappropriate antidiuretic hormone section; four cases of transient postoperative diabetes insipidus; and one case of transient sixth cranial nerve palsy. One patient developed urosepsis postoperatively but recovered fully. A 68-year-old woman with hypertension who presented with a macroadenoma, altered mental status, and hydrocephalus suffered a small stroke perioperatively; she fully recovered after transsphenoidal surgery and ventriculoperitoneal shunt placement. There were no cerebrospinal fluid leaks and no cases of meningitis.

No patient developed new hypopituitarism in the early period.

**FIG. 1.** Bar graph depicting remission rates in relation to tumor size and invasiveness in 115 patients with acromegaly who underwent primary transsphenoidal surgery.
postoperative period. Of the 34 patients with preoperative partial hypopituitarism, 20 experienced improvement of pituitary function gradually after surgery and 14 (all of whom had macroadenomas with persistent postoperative disease) had continued hypopituitarism. The two patients with preoperative panhypopituitarism continued to have the disorder after surgery.

Early postoperative GH levels obtained during Days 2 to 4 were available in 84 patients. Figure 2 shows early postoperative GH in relation to the percentage of patients in remission after surgery. A postoperative GH level of 5 ng/ml or higher (24 patients) was associated with no remission. A postoperative GH level that was less than 3 ng/ml (44 patients) was associated with an 89% chance of long-term remission. However, two patients who had early postoperative GH values of 2 ng/ml or less and initial normalization of IGF-I level later experienced clearly documented recurrence with elevation of IGF-I level. Two others who had an early postoperative level of GH that was 2 ng/ml or lower did not attain normal IGF-I levels and had persistent disease postoperatively.

A higher preoperative GH level tended to correlate negatively with success of surgery. Microadenomas and macroadenomas accompanied by a preoperative GH level of less than 10 ng/ml had remission rates of 90% and 80%, respectively. Rates of remission fell progressively with rising GH to approximately 55% for all tumors with GH of 30 to 50 ng/ml. No patient with a macroadenoma and preoperative GH more than 200 ng/ml was cured by transsphenoidal surgery alone.

The overall recurrence rate after surgery in our series was 5.4%. After the initial surgical cure, no microadenomas recurred, but 7.7% of macroadenomas did recur. All recurrences to date have occurred between 1 and 2.5 years postoperatively.

Outcome After Radiotherapy

Of the 32 patients in our series who had postoperative radiotherapy, 10 (31%) are currently in remission after surgery and radiotherapy only, and an additional three are in remission after radiotherapy and medical therapy with octreotide (two patients) or bromocriptine (one patient). The percentage of patients in whom remission was achieved after radiotherapy rises with the number of years after radiotherapy. The mean duration of time from radiotherapy is 7.4 years in the group in remission (range 1–13 years) and 3.5 years in the group not in remission (range 2 months–6 years). Eleven patients developed new hypopituitarism after radiotherapy from 1 to 6 years later.

Discussion

In this study we obtained current postoperative follow-up data by using strict criteria for biochemical cure in a series of 115 patients who underwent transsphenoidal surgery for acromegaly: normalization of the IGF-I level, which was available in most patients, or a random or glucose-suppressed GH level of less than 2 ng/ml. In our series we found 71% of the patients to be in remission currently after undergoing surgery and adjuvant treatment and 61% of patients to be in remission after undergoing surgery alone. In our series patients who had microadenomas had the best outcome, with 88% cured after transsphenoidal surgery alone. The results of surgical series can be difficult to compare because some include patients who have undergone prior surgery and radiotherapy; however, our results are in agreement with most other transsphenoidal surgical series, which have reported cure rates for transsphenoidal surgery in patients with acromegaly at generally between 60% and 70%. In most prior series, surgical results in patients with microadenomas were considerably better than in those with macroadenomas. For example, in one series there was a 78% cure rate for intrasellar tumors compared with 33% for invasive adenomas, not dissimilar to the results reported here. Prior series have found tumor stage to be the strongest predictor of surgical outcome.

We, too, found that patients with large and invasive tumors had a worse outcome after surgery. Similar to most prior series the majority of our acromegalic patients presented with macroadenomas; invasive adenomas were also common, constituting 29% of our series. Other authors have also reported a worse prognosis the higher the level of preoperative GH. In our series this trend also seemed to occur.

The results of surgical series for acromegaly can also be difficult to compare because the criteria used to define “cure” have varied over the years and between studies. In most prior series the cure rate has been reported based on a postoperative GH level lower than 5 ng/ml; however, in some recent series more strict criteria have been used. In one series an overall remission rate of 52% was reported with the strict criterion of basal or glucose-suppressed GH being less than 2 ng/ml. In another a cure rate of 42% was reported with a mean serum GH level of less than 2.5 ng/ml measured over 4 hours. Recently, in some small series outcome has been examined after surgery based on IGF-I level. Insulin-like growth factor—I, produced in the liver in response to GH, mediates many of the actions of GH. Serum IGF-I concentration remains relatively constant over the day and, therefore, is believed to be representative of integrated 24-hour GH secretion. In most reports, the IGF-I level returns to normal if surgery has been successful. Measurement of IGF-I level is considered an essential part of the biochemical evaluation of this disease, and the IGF-I level should normalize if a bio-
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Chemical cure of acromegaly has been achieved. In a series of 42 patients in whom cure was defined as normalization of IGF-I level, the authors reported a 76% success rate for patients who underwent transsphenoidal surgery and adjuvant therapy, and another study found normalization of IGF-I postoperatively in 17 (59%) of 29 patients with acromegaly.

Although our criteria used to define cure are strict by current standards, evidence suggests that a normal degree of GH suppression after glucose administration when GH is measured with a sensitive assay may be much lower than 2 ng/ml. In most of the 57 patients we studied in detail, IGF-I and glucose-suppressed GH levels measured by RIA were concordant. However, five of our patients had normal IGF-I levels, but their glucose-suppressed GH levels measured between 2 and 3 ng/ml, which was close to but not quite at our cutoff of 2 ng/ml. It is unclear whether our ability to distinguish GH levels near this cutoff in some patients may, in part, be limited by the sensitivity of our current polyclonal GH RIA. It is also unclear whether this apparent lack of adequate GH suppression reflects persistent GH dysregulation that may progress with time to clinically significant active acromegaly. We are currently in the process of determining whether use of a highly sensitive GH assay will lead to a modification of the definition of biochemical cure in postoperative patients with acromegaly.

Our series confirms other reports that demonstrate the low morbidity and mortality rates of the transsphenoidal approach for the treatment of acromegaly. The complication rate reported from a number of series has been summarized by others at 6.7%. Our complication rate was similarly very low at 6.9%, and all of these complications were transient.

The recurrence rate in our series was 5.4% for all tumors: 7.7% for macroadenomas and 0% for microadenomas. Prior series have reported recurrence rates ranging from 14 to 4.3% and as low as 0%. The variation in recurrence rates reported in the literature has likely occurred because the criteria used to define recurrence are not uniform. One other series in which recurrence was defined similarly to us (a failure of the GH level to be suppressed to below 2 ng/ml after administration of glucose subsequent to a normalization) found the recurrence rate to be 8%. Higher recurrence rates reported in the past may have reflected actual persistent rather than recurrent disease that was not detected by less precise testing techniques.

The assessment of early postoperative success by examination of early postoperative GH levels has been used by others and some have found this to be a useful prognostic indicator. In a series of 117 patients, if the early postoperative GH level was lower than 5 ng/ml, a recurrence developed in 4.3% of patients compared with a 21% recurrence if the GH level was 5 to 10 ng/ml. We, too, found that an early postoperative GH level lower than 3 ng/ml was a positive prognostic value, but even at this level up to 11% of tumors did recur and these cases required further treatment. Although we did not examine it systematically, we have not found the early postoperative IGF-I level to be useful for prognostic purposes. As has been shown by others, it can fall gradually in the early postoperative period.

In our series 13% of the patients are currently receiving adjuvant therapy composed of either octreotide or bromocriptine. Most of these patients were not in remission at the time of testing, although most were receiving ongoing adjustments in therapy. Other studies have shown an approximately 20% success rate at suppression of GH to lower than 5 ng/ml with bromocriptine. With octreotide therapy it has been reported that 47% of patients will achieve a normalized IGF-I level with tumor shrinkage demonstrated in up to 57% of patients. In addition, octreotide may improve symptoms and can improve pulmonary and cardiac status. Octreotide therapy seems quite effective when surgery has failed as the primary treatment or as an adjuvant to radiotherapy to control GH levels until radiotherapy has become effective. In our patient population medical therapy with octreotide is becoming more frequently chosen as the primary adjuvant therapy especially in younger patients if surgery has been unsuccessful.

In our overall series of 115 patients, 32 received radiotherapy postoperatively and 13 are currently in remission, three with additional medical therapy. Prior series have demonstrated in general that approximately 50% of patients achieve circulating GH levels of less than 5 ng/ml at 10 years after receiving conventional radiotherapy. However, a recent report found that only 5% of patients evaluated for a mean of 6.8 years after conventional (35 patients) and proton-beam (three patients) radiotherapy experienced normalized IGF-I levels. It may be that assessing biochemical outcome after radiotherapy with IGF-I levels will reveal a significantly lower success rate than previously reported when using GH criteria to determine disease status. In our series, all 32 patients had available current IGF-I levels assessing their status after radiotherapy, and currently 10 (31%) of the 32 have controlled disease with surgery and radiotherapy only. This low percentage may in part reflect the fact that many patients are still within the first few years after radiotherapy.

Conclusions

In this study we provide long-term postoperative follow-up endocrinological evaluation in a large cohort of patients who underwent transsphenoidal surgery for acromegaly by using IGF-I measurements and strict GH suppression criteria to define biochemical cure. We were able to obtain current laboratory data in 99 of 115 patients with a mean length of follow up lasting 5.4 years. Fifty-seven patients were available to have a full current evaluation and laboratory testing performed by us. In this experience of a single surgeon (K.D.P.), transsphenoidal surgery provided an excellent chance of long-term cure in patients with microadenomas—88%. Surgery alone is successful in most patients with noninvasive macroadenomas; however, most patients with invasive macroadenomas will require adjunctive therapy. We found that recurrences over the follow-up period in this series were uncommon when biochemical remission was clearly documented postoperatively. Future studies are planned to determine how testing with a highly sensitive GH assay will affect the definition of biochemical cure after transsphenoidal surgery in patients with acromegaly.

J. Neurosurg. / Volume 89 / September, 1998

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Acknowledgments

We thank Mr. Robert Sundeen for expert technical assistance with growth hormone measurements and Novartis Pharmaceuticals for assistance with funding of the clinical testing and IGF-I measurements.

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Manuscript received September 15, 1997.
Accepted in final form April 30, 1998.
This research was funded in part by Grant No. RR-00645 from the National Institutes of Health, National Center for Research Resources.
This paper was presented in part at the 79th Meeting of The Endocrine Society, June 11-14, 1997, Minneapolis, Minnesota (Abstract P3-51).
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